Remarks

Claims 1-26 are pending in the present application. Claims 2, 4, and 14-26 are withdrawn from consideration as being directed to a non-elected invention. Currently under prosecution are claims 1, 3, and 5-13, directed to Group II, with election of SEQ ID NO:10 as a species of molecule and inflammation as the disease condition. These claims are rejected in the instant action.

Applicants respectfully request reconsideration of the application, withdrawal of all rejections, and allowance of the application in view of the amendments and remarks below.

Information Disclosure Statement

Applicant thanks the Examiner for the reminder that citations in the Specification do not act as a proper Information Disclosure Statement and should be submitted for consideration of the Office in proper format. Applicant will submit an Information Disclosure Statement shortly.

Specification

Applicant thanks the Examiner for the reminder that the Examiner has not conducted a check of the Specification sufficient to determine the presence of all minor errors. Applicant thanks the Examiner for this reminder and has attended to a review of same.

Claim rejections

35 U.S.C. § 102(e)

Claims 1, 3-8, 10, 11, and 13 are rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. 6,156,727 issued to Garber, in light of Selzman *Ann Thorac Surg* 2001;71:2066-2074.

The Examiner contends that the Applicants claim a method for effective treatment of inflammation comprising providing to a recipient a physiologically effective amount of a pharmaceutical composition of a molecule that targets SR-BI/CLA-1, and Applicants elected SEQ ID NO:10 as the molecule. The Examiner alleges that Garber discloses the same peptide as SEQ ID NO:1, therein called 18A-Pro-18A, and the composition is administered to fat sensitive mice for atherosclerosis lesions; according to the Examiner, atherosclerosis lesion is caused by inflammation as illustrated by Selzman.

Applicant traverses the anticipation rejection.

Claims 1, 3, 5, 8, and 11

With regard to the teachings of Selzman, Applicant submits that the Examiner has drawn incorrect conclusions with regards to atherosclerosis being "caused" by inflammation from this art. The Examiner states that Selzman teaches that "[a]therosclerosis lesion is caused by inflammation as illustrated by Selzman (Figure 3 and page 2072, column 2." However, it is respectfully submitted that Selzman does not teach that all phases of atherosclerosis and the formation of atherosclerotic plaques is caused by inflammation. Rather, Selzman teaches that atherosclerosis is a disease that has many phases, including non-inflammatory phases, and can be initiated in childhood. Specifically, Selzman teaches that "[a]therosclerosis is a pathologic condition that cannot be defined as a single disease entity." See page 2066 first column. Selzman makes clear that "[t]he initial or type I lesions, consisting of lipid deposits in the intima, have been well documented in infants and children. Fatty streaks, or type II lesions, are visible as yellow-colored streaks, patches, or spots on the intimal surface of arteries. Microscopically, these lesions are characterized by intracellular accumulation of lipids." See page 2066 first column.

Selzman then goes on to discuss the "lipid hypothesis" of atherosclerosis. See 2066, column 2. Namely, that "cellular changes in arteriosclerosis are reactive events in response to lipid infiltration." In other words, there is an initial injury phase where lipids build up on the wall of the artery, likely in response to high blood lipid levels such as high LDL, and after some time, at some point, triggers an inflammatory reaction. Selzman teaches, "[t]he influence of lipids on cardiovascular disease is clearly evidenced in patients with genetic hyperlipidemias, in which homozygous individuals rarely live beyond 26 years. Antilipid therapy is one of the few strategies that has induced regression of arteriosclerosis in randomized, prospective clinical trials." See page 2066, column 2. Selzman teaches that lipid buildup is a stage of arteriosclerosis. According to Selzman, an inflammatory response is eventually provoked by this buildup of lipids on the arterial wall, where "[e]ndothelial disruption or dysfunction allows for adhesion and transmigration of circulating monocytes, platelets, and T lymphocytes." See page 2067 column 2.

Selzman thus teaches that in arteriosclerosis, there is an initial lipid accumulation phase, which eventually leads to injury of the endothelium leading to an inflammatory response. See page 2069 column 2. Selzman hypothesizes intervening into this initial injury phase, i.e., that "therapeutic efforts should [be targeted to] interrupt the vessel's response to injury." Page 2069 column 2. At page 2071, second column, Selzman teaches that "a variety of insults will initiate a cascade of events that converge to one or more dominant events [inflammation.]" In other words, there are arteriosclerotic phases that precede the inflammation stage.

In conclusion, the applicable teachings of Selzman are that "antiatherosclerosis strategies aim to eliminate injury **OR** the vessel's pathologic response to that injury. Primary prevention remains the most feasible option." (emphasis added.) See page 2073 column 1.

It is submitted, therefore, that atherosclerosis does not involve inflammation at all stages, and early stages are characterized by lipid deposition which leads to vessel injury and dysfunction, which then the endothelium reacts to with an inflammatory response. Intervention by therapeutic agents may occur either at the early stage, to eliminate the injury in the first place (i.e., preventing lipid buildup by, e.g., lowering LDL or total lipid in the blood) **OR** to address the inflammatory response provoked by the injury.

Turning to the teaching of Garber, Garber teaches the use of SEQ ID NO:1 for the purpose of preventing lipid buildup. Garber teaches that it has been found that regression of experimentally induced atherosclerosis may be achieved by the administration of hypolipedemic agents. See Col. 1 lines 27-31. Garber teaches that HDL functions to inhibit the development of atherosclerosis by acting as a sink for cholesterol. See Col. 1 lines 36-39. Garber also teaches that high levels of LDL are the main cause of hypercholesterolemia. See Col. 2 lines 27-28.

Garber then teaches that apolipoproteins' main function appears to be solubilizing lipids in circulating plasma, and the mechanism appears to be via specialized helical domains (amphipathic helial domains) that interact with the lipids. Col. 2, lines 59-67. Apolipoprotein A-I (ApoA-I) appears capable of effluxing cholesterol from cholesterol loaded cells and may have a direct effect on atherosclerosis. Col. 3 lines 1-5. Garber teach that mice expressing ApoA-I are resistant to diet-induced atherosclerosis. In particular, a mouse strain C57BL/6 is most susceptible to diet-induced atherosclerosis, and in particular, transgenic C57BL/6 mice overexpressing ApoA-I were protected from the development of fatty streak lesions.

Therefore, Garber teach that cholesterol-binding protein ApoA-I can protect against the formation of lipid deposits in mice susceptible to diet-induced atherosclerosis. Col. 3 lines 51-60. Garber teach that peptide 18A-Pro-18A (SEQ ID NO:1) closely mimics many of the *in vitro* properties of human ApoA-I. Col. 6 lines 37-42. Garber teaches that 18A-Pro-18A is an amphipathic helical peptide having many of the same functions ApoA-I and HDL, particularly in regard to clearing cellular cholesterol and phospholipid from cholesterol-loaded cells. Col. 7 lines 26-29.

Importantly, Garber demonstrates that when radiolabelled 18A-Pro-18A was injected into 57BL6/J mice, that the radiolabel was present exclusively in the HDL. In other words, the peptide was demonstrated to be partitioning to lipid exclusively. In Example 3, 18A-Pro-18A was shown, in Garber's words, to "inhibit[] diet-induced lipid accumulations in these animals." In Example 4, Garber teaches that "the peptides disclosed herein [including 18A-Pro-18A] are capable of inhibiting the production of atherogenic lipoproteins." In Example 11, Garber teaches that "[a]therosclerosis **protection**" is achieved by "amphipathic helical peptides." Col. 13 lines 19-20. (emphasis added.)

Applicant's extensive review of the teachings of the applied references, Selzman and Garber, shows that atherosclerosis is a complex disease which occurs in several phases, several of which **do not comprise an inflammatory response**. Selzman teaches an initial lipid accumulation phase, leading eventually to injury of the endothelium followed by an inflammatory response. Thus importantly atherosclerosis not "caused" by inflammation as the Examiner asserts! Atherosclerosis is defined as including the early, lipid-accumulation phase leading to inflammation.

In fact Selzman teaches that "antiatherosclerosis strategies aim to eliminate injury **OR** the vessel's pathologic response to that injury. Primary prevention remains the most feasible option." In other words, atherosclerosis treatments include treatments to minimize or prevent injury to vessels.

Garber teaches such an injury-elimination strategy. The peptide 18A-Pro-18A is taught to be an amphipathic helical peptide having many of the same functions ApoA-I and HDL, particularly in regard to clearing cellular cholesterol and phospholipid from cholesterol-loaded cells. Garber demonstrates 18A-Pro-18A is sequestered into HDL upon administration and that

it functions to "inhibit[] the production of atherogenic lipoproteins," and that "[a]therosclerosis protection" is achieved by "amphipathic helical peptides."

Therefore the Examiner is incorrect in his assertion that atherosclerosis is "caused" by inflammation and that an agent that functions to prevent or treat atherosclerosis is necessarily acting in an anti-inflammatory manner. Selzer teaches multiple stages of atherosclerosis including an injury phase, which can be caused by hyperlipidemia. Garber teaches 18A-Pro-18A as an agent to protect from the injury phase of atherosclerosis and teaches that this peptide functions to inhibit production of atherogenic lipoproteins which can form deposits on arteries in the initial phase of atherosclerosis. No teaching exists and indeed, no anti-inflammatory effect can be observed under the conditions tested by Applicants, i.e., administration of 18A-Pro-18A peptide (among others) to C57BL/6 mice fed a high fat diet, showing inhibition of diet-induced lipid accumulations in these animals, and/or creation of C57BL/6 transgenic for 18A-Pro-18A (or related peptides), again, showing inhibition of diet-induced lipid accumulations in these animals.

Therefore it is respectfully submitted that the references cited do not, in fact, teach 18A-Pro-18A as an anti-inflammatory agent, merely as an atherosclerotic protective, one, acting through the mechanism of binding to cholesterol and other phospholipids through its amphipathic helical lipid-binding character and demonstrating inhibition of diet-induced lipid accumulations in mice. No anti-inflammatory role for these peptides was demonstrated. Therefore, the applied references do not teach every element of the claim, as required for a proper anticipation reference. See MPEP 2131.

Neither do these references teach anti-inflammatory properties of 18A-Pro-18A by inherency. "The very essence of inherency is that one of ordinary skill in the art would recognize that a reference unavoidably teaches the property in question." See *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981) ("Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient."); *Hitzeman v. Rutter*, 243 F.3d 1345, 1355 (Fed. Cir. 2001). As pointed out above, an anti-atherosclerotic agent may act to inhibit atherosclerosis by a non-inflammatory mechanism, which is submitted, is the case here. Here it has not been demonstrated that Garber and Selzman "unavoidably" teaches anti-inflammatory properties for 18A-Pro-18A.

Reconsideration is respectfully requested.

Claims 7 and 10

With regard to rejection of claims 7 and 10, the Examiner states that since 18A-Pro-18A competes with HDL for binding. For the reasons given above, for the rejection of claims 1, 3, 5, 8, and 11, this rejection cannot stand.

Claim 7

The Examiner also points out, for claim 7, that 18A peptide was demonstrated in Garber to inhibit the LPS-induced toxicity in mice. It is respectfully pointed out that 18A peptide is not claimed herein. 18A peptide is an 18-mer. SEQ ID NO:10 is a 37-mer. Therefore, this rejection is inapposite and withdrawal of same is respectfully requested.

35 U.S.C. § 103(a)

Claims 1, 3, and 5-13 are rejected under 35 U.S.C. § 103(a) as being obvious over U.S. 6,156,727 issued to Garber, in view of U.S. 6,664,230 issued to Fogelman in light of Selzman Ann Thorac Surg 2001;71:2066-2074. The Examiner maintains that Garber and Selzman teach as specified above for the anticipation rejection. The Examiner alleges that Fogelman teaches that peptide 18A (also disclosed by Garber) in enantiomeric form is a D-amino acid and that such peptides are more resistant to digestion in the stomach.

According to the Examiner it would have been obvious to one of ordinary skill in the art to combine the teachings of Garber and Fogelman to arrive at the instant invention as Garber allegedly teaches the method of treating inflammation with the elected peptide and Fogelman teaches the peptides wherein L-isomers were replaced with D isomers.

As discussed above for the anticipation rejection, and incorporated herein, it is submitted that in fact Garber in light of Selzman does not teach the instant peptide for treatment of inflammation. Briefly, it is respectfully submitted that the references cited do not, in fact, teach 18A-Pro-18A as an anti-inflammatory agent, merely as an atherosclerotic protective, one, acting through the mechanism of binding to cholesterol and other phospholipids through its amphipathic helical lipid-binding character and demonstrating inhibition of diet-induced lipid accumulations in mice. No anti-inflammatory role for these peptides was demonstrated.

Therefore, the applied references do not teach every element of the claim, as required for a proper anticipation reference. See MPEP 2131.

With regard to claims 9 and 12, teaching D amino acids, Fogelman does not teach the missing element, i.e., that 18A-Pro-18A is useful for treating inflammation. Therefore, this rejection cannot stand.

For the reasons set forth above, Applicant respectfully submits the claims as filed are allowable over the art of record and reconsideration and issuance of a notice of allowance are respectfully requested. As said above the double patenting rejection will be addressed once all other issues have been overcome. If it would be helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned.

This constitutes a request for a two-month extension of time and an authorization to charge all fees therefore to deposit account No. 19-5117, if not otherwise specifically requested. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to deposit account No. 19-5117.

Respectfully submitted,

Date: December 21, 2010

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